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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/286,874	04/06/99	GRAHAM F	ADVEC9

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EXAMINER	
BRUNOVSKIS,P	
ART UNIT	**PAPER NUMBER**
1632	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/286,874	Applicant(s) GRAHAM ET AL.	
	Examiner Peter Brunovskis	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *5-7 and 10-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,9 and 13-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed 4/26/01 has been entered. Amendment of claim 13 and entry of new claim 15 is acknowledged. Claims 1-14 are pending in the instant application. Claims 5-7 and 10-12 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7. Claims 1-4, 8, 9, and 13-15 are under examination in the instant application.

Applicant's arguments filed 4/26/01 will only be considered or addressed to the extent that they apply to the claims under examination. Unless otherwise indicated, arguments directed to rejections rendered moot by Applicants amendments or Examiner's withdrawal will not be further addressed or acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 13-14 remain indefinite and claim 15 is indefinite under 35 U.S.C. 112, second paragraph, for the reasons set forth in the Office Action of 10/24/00 and for the reasons set forth

below as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and dependent claims) remains indefinite in its recitation of the term "substantially devoid" since it is not clear how this term is defined or what its metes and bounds are. Applicants response is not persuasive essentially because it is either directed to passages in the specification reciting "deleting most is not all viral coding sequences" (p. 2, lines 7), whose metes and bounds are unclear or to passages directed at embodiments lacking viral coding sequences altogether (i.e. p. 4, lines 11-12 and 17-18). Amending the claims to recite "devoid", "completely devoid" of "lacking" would obviate the rejection.

Claim 13 remains indefinite in its recitation of the phrase, "essentially no infectious particles of helper virus" in part (c) since the specification is unclear as to the metes and bounds of this phrase so as to allow one to determine whether their invention is infringing upon this claim, particularly since there are no quantitative values or cutoff values recited. The response has failed to address the rejection set forth in the Office Action of 10/24/00 because the amendment and the response only obviate the indefiniteness as directed to the limitation "efficient expression" in part (b).

Claim 13 (and dependent claim 14) remains indefinite in its recitation of the limitation "capsid proteins encoded by said helper adenovirus" in part (c) due to insufficient antecedent basis for this limitation in the claim. Changing the phrase "said series of adenoviruses expressing a

different set of capsid proteins" in part (a) to --said series of adenoviruses encoding a different set of capsid proteins-- would obviate the problem.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining enablement are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Newly entered claim 15 is drawn to a adenoviral vector gene delivery system comprising helper adenoviruses Ad-2 and Ad-5 from the same subgroup that do not give rise to cross-reactive antibodies when administered to a subject *in need of* said delivery system (emphasis added). When read in light of the specification the claimed composition is interpreted as a composition for gene therapy, inasmuch as the specification fails to provide any other use of said system in the context of a subject *in need of* such.

Given that the adenoviral vector delivery system of claim 15 is predicated on its ability to not give rise to cross reactive antibodies when administered to a subject in need of said system for therapeutic use, the critical question is whether the specification provides a sufficiently enabling disclosure commensurate with therapeutic use. At the time filing, successful use of gene therapy was not routinely obtainable by those skilled in the art. W. French Anderson, one skilled in the art, recently concluded: "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human diseases [Nature, vol. 392:(Supp.), 1998, p. 25, first paragraph]...[s]everal major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make" (p. 30, next to last paragraph). Concurring with Anderson, Verma and Somia state that "[t]he

Achilles heel of gene therapy is gene delivery...and [t]hus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (Nature, vol. 389, 1997, p. 239, col. 3, 2nd paragraph)...[a]lthough more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239, col. 1, 2nd paragraph).

Despite being considered by some as the "gold-standard" for gene transfer, adenoviral vectors were recognized at the time of filing as yet to have been developed to overcome the problems described by Anderson and Verma. Curiel reviewed the state of the adenoviral vector art as it relates to gene therapy as follows:

> "To date, several groups have sought to exploit the fundamental advantages of adenovirus by using it in specific contexts where the recognized limitations were judged to be less important. For example, it was thought that the issue of the widespread tropism of the virus could be circumvented by administering the vector by direct injection, particularly in the context of tumors. However, in phase I human trials, dissemination beyond the injected site was found. Application to "compartmentalized" disease has also met with problems. For example, poor gene transfer efficiency has been noted following administration into the pleural space for therapy of mesothelioma, and in the peritoneum, effective use of antitumor gene therapy has been limited by concurrent gene transfer of the liver with subsequent toxicity. Further limitations have arisen in the application to pulmonary disease. Here, prior clinical experience had indicated that the virus had a natural tropism for the respiratory tract; therefore, direct administration of vector to the airways for cystic fibrosis therapy seemed a rational approach. In reality, the achieved levels of gene transfer were lower than expected, because differentiated airway epithelial cells lack sufficient adenoviral receptors and the integrins required for viral internalization. Therefore, even in these apparently favorable anatomic locations there is a strong case for developing a vector with cell-specific targeting properties" (p. 159, Ann. NY Acad. Sci., 886:158-171, 1999).

Furthermore, in reviewing the use of adenoviral vectors for gene therapy of cancer, Gomez-Navarro et al. taught that "transduction efficiencies of presently available vectors have been shown to be inadequate. Even in the context of closed compartment delivery, it has not been possible to modify a sufficient number of tumour cells to achieve a clinically relevant tumoral response" (p. 873, right col., Eur. J. Cancer, 35(6):867-885, 6/99). The claimed invention is directed to just one of the many problems associated with enabling the practice of adenoviral vectors for therapeutic use, namely that directed to reducing immunogenicity upon repeat administrations. However, the prior art of record points to other issues relating to targeting and obtaining adequate expression that are not sufficiently addressed in the instant disclosure so as to overcome the problems in the prior art. In view of the failures associated with attempts to treat diseases by gene therapy as taught by Anderson and Verma, and the problems and challenges concerning use of adenoviral vectors as taught by Curiel and Navarro-Gomez, in the absence of *relevant* working examples directed to therapeutic use (as in the instant case), and *specific* guidance regarding routes of delivery, nature of transgenes and diseases, any attempts to use the claimed adenoviral vector delivery system in a therapeutic setting would be highly unpredictable.

Further, although the specification *does* provide an enabling disclosure for an adenoviral gene delivery system comprising helper adenoviruses Ad-2 and Ad-5 from a common subgroup (i.e. subgroup C) that do not give rise to cross-reactive antibodies when administered to a subject *in need of* said system, the specification does not provide sufficient guidance or reasonable

expectation of success for enabling the use of other helper adenoviruses within subgroup C or within the other 5 adenovirus subgroups (i.e. A, B, D-F).

Applicant's arguments filed 4/26/01 have been fully considered to the extent that they apply to the newly rejected subject matter but they are not persuasive. With regard to the immunological aspects of the claimed invention as addressed on pages 7-11 of the response, the following arguments are noted. First, the response suggests that in view of he lack of cross reactive antibodies between closely related Ad2 and Ad5 serotypes, it would reasonably follow that more widely divergent serotypes would not produce cross reactive antibodies. While such a generalization may appear reasonable with respect to other subgroup C members, the evidence of record fails to provide a reasonable showing that the same pattern of cross-reactivity (or rather lack thereof) would similarly apply to other much less characterized adenoviral subgroups. In fact, in reviewing immunomodulation strategies for enhancing adenoviral gene expression in vivo, Wilson and Kay taught that secondary administration of the same *or related* adenoviral vectors precludes gene expression on account of neutralizing antibodies generated from the previous administration (p. 887, right col.; Nat. Med., 1(9):887-889, 9/95).

Further, although it may require routine experimentation to determine operative and inoperative combinations as suggested in p. 10 of the response, enabling the subject matter of claim 15 as it relates to administration in a subject in need of such is essentially predicated on whether the vector delivery system comprising helper serotypes from the same adenoviral subgroup with potentially non-equivalent cell tropisms can be used in a method of treatment

where targeting and expression are critical. Furthermore, the specification fails to provide sufficient guidance concerning the extent to which ITRs or packaging signals from different uncharacterized serotypes would necessarily be complemented by other members of the same subgroup as in the case with Ad-2 and Ad-5, not produce cross-reactive antibodies, *and* produce a clinically beneficial effect in a subject in need of said vectors.

The response appears to partially address the issue of ITR/packaging signal/helper complementation, however, it does not sufficiently address the critical issues in this regard. For example, the basis for the rejection as previously set forth in the context of vector compositions without reference to therapy was not directed to the question of whether cis-acting ITR/packaging signal elements affect the ability of viruses to express transgenes or to design of constructs allowing for a determination of whether complementation would be achievable in a given situation. The specification only provides guidance or working examples involving complementation between two subgroup C serotypes in production of chimeric gutless adenovirus vectors. There is no evidence of record indicating broad complementation of cis-acting signals by capsid proteins from other closely members of the same subtype and the evidence of record fails to provide support for the generalization set forth at the top of p. 14 in the response that "there is a reasonable expectation of success to combine many, if not most, serotypes where the helper Ad originates from one serotype and the hd-Ad originates from a different serotype", particularly since this issue has only been addressed in one specific context (i.e. Ad-2/Ad-5). In view of teachings in the art, as exemplified by Wilson above, there is not a sufficient basis for concluding

that closely related members within any of the different adenoviral subtypes can be sufficiently complemented with one another to: (1) produce a chimeric vector; (2) to not cross-react; and (3) to maintain appropriate targeting and expression commensurate with a therapeutic benefit.

With regard to issues of tropism of Ad serotype groups (p. 14-16), Applicants arguments directed to infectivity of Ad2/Ad5 only address one small aspect of targeting in general without addressing the specific problems relating to targeting within the context of therapeutic use. The fact that *certain* serotypes (i.e. Ad-2/Ad-5) may infect common subsets cells (albeit in a relatively ubiquitous manner), it does not provide a basis for enabling the broad scope of embodiments directed in many cases to much less characterized Ad serotypes when compared to the serotype C strains of the claimed invention. In fact, the relatively promiscuous infectivity of adenoviruses and of gene therapy vectors in general continues to represent the "Achilles heel of gene therapy" (i.e. effective targeting; see e.g. Verma et al., Nature, 389:239-242) and one of the chief areas in adenoviral vector development (see e.g. Curiel, Ann. NY Acad. Sci., 886:158-171, 1999). The teachings in Curiel as directed to adenoviral tropisms and the problems associated *even with localized vector administration* using well characterized adenoviral serotypes, as disclosed in the instant application (i.e. Ad-2/Ad-5), underscore the problems of enabling the broad range of chimeric adenoviral embodiments of the instant application for therapeutic use.

With regard to the issues relating to the ability of trans packaging factors and cis packaging signals from different serotypes or subgenera to function together (p. 16-18), in the context of the intended use limitations directed to therapeutic use, Applicants attention is directed

to the above arguments relating to question of *how to use, in addition to how to make.* On the other hand, it is noted for the record that Applicants statements concerning recognition of compatibilities and differences between Ad serotypes are not probative since they merely provide unsubstantiated assertions (without *specific* evidence) that in view of such differences "one of ordinary skill in the art can derive the critical teaching from the Applicants' specification and, without further undue experimentation, devise an appropriate sequence of helper Ads to function sufficiently with a particular hdAd...[further claiming that]...modifications to either helper or hd genome can be achieved by methods well known in the art to improve the performance and compatibility of a particular combination of helper and hdAds of different serotypes" (p. 17, middle). Neither of these statements sufficiently or specifically address the nature of the asserted "critical teaching" or provide evidence that such "modifications" were widely known or practiced at the time of filing within the context of these admitted "differences in compatibility" for the purpose of constructing functional helper/hdAd combinations in the context of therapy. Again, the issue of cis-acting signals and their effect on transgene expression is not important here, but rather the issue of compatibility at the level of packaging functional chimeric adenoviruses. As correctly pointed out by Applicants (top of p. 19), "[w]hen considering the undue experimentation factors, the Examiner's analysis 'must consider all the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole'". Therefore, a fully enabled disclosure must be viewed in the context of not only making, *but of using in a manner commensurate with the scope of the claimed subject matter.* In view of the nature of the

art, the lack of specific guidance, and the paucity of working examples commensurate with the scope of the instant invention, as claimed, the response fails to overcome the *prima facie* case for lack of enablement as directed to the therapeutic intended use limitation recited in the rejected claim.

Deletion of the phrase "and the serotypes of said at least two helper adenoviruses do not give rise...to a subject in need of said adenoviral vector gene delivery system" would obviate this rejection. Alternatively, substituting the above phrase with --wherein said at least two helper adenoviruses do not give rise to cross-reactive antibodies-- would also obviate the rejection, in view of the fact that it would not require undue experimentation to determine whether a given helper adenovirus within a given subtype produces cross-reactive antibodies and given the fact that the claimed vector compositions are enabled for use in delivery of genes in cell culture.

Allowable Subject Matter

Claims 8 and 9 are allowed. Claims 1-4 and 13-15 are free of the art and would be allowable upon amending the claims to overcome the 35 U.S.C. 112, 1st paragraph (cl. 15) and 2nd paragraph rejections (cl. 1-4, 13-15). The closest prior art is drawn to gutless adenovirus vectors as taught by Graham et al. (WO 98/13510, 4/2/98; IDS document filed 4/26/01) and the use of adenoviral vectors circumventing anti-adenoviral neutralizing immunity by sequentially readministering adenoviral vectors packaged with alternate serotypes of the same or different adenoviral subgroups. of different serotypes as taught by Mack et al (Hum. Gene Ther., 8:99-109,

1/1997; IDS document filed 7/12/99) and Kass-Eisler (Gene Ther., 3(2):154-162, 2/96; IDS document filed 7/12/99), respectively. Graham et al. discloses an adenovirus vector delivery system comprising a helper dependent adenovirus vector, hdAd (Ad5-based), comprising a genome substantially devoid of adenoviral protein coding sequences (i.e. gutless vectors), but encoding a gene and expression control sequences, and an Ad5 helper adenovirus of the same serotype encoding all functions required to facilitate hdAd genome packaging and replication, but which helper adenoviruses themselves do not package into infectious virus particles due to cre recombinase-mediated deletion. However, Graham et al. does not teach or suggest the use of multiple helper adenoviruses of different serotype relative to the helper dependent vector for the purpose of creating different and distinct genetically identical adenoviral vectors wherein each member of the series has a different serotype conferred by the helper or wherein the members of the series do not produce cross-reactive antibodies. Kass-Eisler et al. further suggests that "if a battery of 6-12 different adenovirus vectors were generated based on different serotype backbones...it may be possible to administer a therapeutic gene a minimum of 6-12 times" (p. 160, right col.). However, absent hindsight evidence, neither Graham et al., Mack et al., nor Kass-Eisler teach, suggest, or render as obvious the use of *a series of helper adenoviruses of a different serotypes relative to the helper dependent vector* in combining these references.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda can be reached at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to the Patent Analyst, Patsy Zimmerman whose telephone number is (703) 308-8338.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632

Deborah Crouch

DEBORAH CROUCH
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